FDA Questions for Circulatory System Devices Panel

File: P010012/S026 (COMPANION)
Sponsor: Guidant
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Decision Questions

Hospitalization Definition

The definition of hospitalization, part of the primary endpoint, was modified during the course of the COMPANION clinical trial. As stated in section 2.2.1 of the approved COMPANION investigational plan,

"…all-cause hospitalization is defined as admission to a hospital for any reason. In addition, this endpoint will include emergency room visits (or unscheduled office visits) that result in treatment with intravenous inotropes or vasoactive drugs."

However, the definition of hospitalization that was used in the analysis for this submission was:

"…hospitalizations for any reason that required the patient to be in the hospital for a period of time in which there was a calendar date change or outpatient infusions of intravenous vasoactive or inotropic therapy exceeding four hours."

Data is not available to allow calculation of the primary endpoint based on the original definition. Additionally, hospitalizations for device implant, including elective implants for OPT patients, were not included in the analysis.

1) **Please comment on whether modifications to the hospitalization definition impact the interpretation of the primary endpoint.**

The COMPANION statistical plan requires that consistency be observed across the primary and secondary endpoints in order to make conclusions on any one endpoint.

2) **Please comment on the impact of modifications to the hospitalization definition on the interpretation of the secondary endpoint of mortality.**

Indications for Use

The sponsor is seeking approval to expand the indicated patient population for their CRT-D devices. In addition, within the Indication for Use statement, the sponsor is seeking approval to include claims of benefit with CRT-D for the primary composite endpoint from COMPANION as well as the secondary endpoint of mortality. The sponsor's proposed Indications for Use statement reads as follows:

> *Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with moderate to severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF </= 35%) and QRS duration >/= 120 ms.*
>
> *Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) have demonstrated the following outcomes in the indicated population specified above:*
>
> ?? *Reduction in risk of all-cause mortality or first all-cause hospitalization*
> *Note: Hospitalization is defined as administration of IV inotropes or vasoactive drugs > 4 hours (outpatient or inpatient), or admission to a hospital that includes or extends beyond a calendar date change.*
> ?? *Reduction in risk of all-cause mortality*
> ?? *Reduction of heart failure symptoms*

3) Are the data from the COMPANION clinical trial sufficient to support an expanded patient population for the sponsor's CRT-D devices?

4) With respect to statements in the Indications for Use regarding the primary endpoint:

a. Are the data from COMPANION sufficient to support claims based upon the primary endpoint results?

b. If so, please comment on whether the language of the proposed Indications for Use statement adequately describes this endpoint. In particular, please discuss whether the term "all-cause hospitalization" is appropriate.

5) With respect to statements in the Indications for Use regarding the secondary endpoint of mortality, are the results from the COMPANION clinical trial sufficient to support a mortality benefit claim for the sponsor's CRT-D devices in the COMPANION population?

Labeling Questions

Hospitalizations

Characterization of the total number of hospitalizations and time spent in the hospital for OPT and CRT-D patients may be useful information for patients and physicians. When implant hospitalizations were included in this analysis, CRT-D patients experienced more hospitalizations and spent more days in the hospital compared to OPT patients.

6)

- **a. Please comment on whether the CRT-D labeling should characterize the total number of hospitalizations and length of time patients spent in the hospital for the CRT-D and OPT arms of the COMPANION trial.**
- **b. If so, please comment on whether device implant hospitalizations should be included as part of that analysis.**

Adverse Events

Please refer to the section of the clinical review (pages 15 through 20) which discusses adverse events for the COMPANION trial. Adverse event comparisons between the CRT-D and OPT arms of the trial may be clinically meaningful to patients and physicians. The sponsor's proposed labeling presents the adverse events from these two groups separately.

7) Please comment on whether the CRT-D labeling should present adverse events from the CRT-D and OPT arms of the COMPANION trial in a consolidated manner that would allow their comparison.

Withdrawals

The dataset used to calculate the primary and secondary endpoints included data from patients who had withdrawn from the COMPANION trial.

8) Please comment on whether data obtained from patients after withdrawal should be used in any of the analyses described in the device labeling.